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Title: Population pharmacokinetic model of canrenone after intravenous administration of potassium canrenoate to paediatric patients

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Keywords

Potassium canrenoate, canrenone, paediatrics, neonates, population pharmacokinetics

What's Known on This Subject

Little is known about the pharmacokinetics of potassium canrenoate/canrenone in paediatric patients

What This Study Adds

A population pharmacokinetic model has been developed to evaluate the pharmacokinetics of canrenone in paediatric patients who received potassium canrenoate as part of their therapy in the intensive care unit.

Research Support

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Abstract

Objectives: To characterize the population pharmacokinetics of canrenone following administration of potassium canrenoate in paediatric patients.

Patients and Methods: Data were collected prospectively from 23 paediatric patients (2 days to 10 years of age; median weight 4 kg, range 2.16-28.0 kg) who received intravenous potassium canrenoate (K-canrenoate) as part of their intensive care therapy for removal of retained fluids e.g. in pulmonary oedema due to chronic lung disease and for the management of congestive heart failure. Plasma samples were analysed by HPLC for determination of canrenone (the major metabolite and pharmacologically active moiety) and the data subjected to pharmacokinetic analysis using NONMEM.

Results: A one-compartment model best described the data. The only significant covariate was weight (WT). The final population models for canrenone clearance (CL/F) and volume of distribution (V/F) were CL/F (L/hr) = 11.4 × (WT /70.0)$^{0.75}$ and V/F (L) = 374.2 × (WT/70) where WT is in kg. The values of CL/F and V/F in a 4 kg child would be 1.33 L/hr and 21.4 L, respectively, resulting in an elimination half-life of 11.2 hr.

Conclusions: The range of estimated CL/F in the study population was 0.67 - 7.38 L/hr. The data suggest that adjustment of K-canrenoate dosage according to body weight is appropriate in paediatric patients.

Introduction

Spironolactone and potassium canrenoate (K-canrenoate), are commonly used in paediatric patients with clinical disorders such as pulmonary oedema, congestive heart failure and hypertension[1,2]. Because of its low solubility in aqueous fluids, spironolactone is only available in per-oral formulation for clinical use. Tablets are licensed in the UK for use in children ≥1 year. An oral suspension may be extemporaneously prepared by crushing tablets or obtained as a 'specials' formulation and as such is an unlicensed use. K-canrenoate is the potassium salt of the γ-hydroxy acid, obtained by opening the lactone ring of canrenone, the major dethioacetylated metabolite of spironolactone. Because of its aqueous solubility, K-canrenoate, is used as an injectable aldosterone antagonist with similar therapeutic activity to spironolactone[3,4,5]. It is not licensed for use in children or neonates in the UK but is frequently used for short-term parenteral treatment in paediatric patients when oral treatment with spironolactone is difficult or not possible[6].

Much of the available information relating to dosage of diuretics in paediatric patients, in particular neonates, is derived from studies conducted in adults[1]. Doses of spironolactone (0.7 x potassium canrenoate) have been proposed[2,6,7] taking account of the higher potency of spironolactone on a mg basis.

Despite the relatively widespread use of spironolactone and K-canrenoate in paediatric patients, there are no available data on the pharmacokinetics of these two medications in this population. In 2003, spironolactone was placed on the US National Institute of Health's list of drugs requiring paediatric investigation[8] and in 2007, it was also included in the European Medicines Agency's priority list of off-patent medicines that require assessment in children[9].

Therefore, the aim of the present study was to investigate the pharmacokinetics of

canrenone after IV administration of K-canrenoate to neonates/infants/children for management of retained fluids (e.g. due to chronic lung disease or congestive heart failure).

Patients and Methods

Patients and data collection

The study was approved by the Research Ethics Committee, Queen's University Belfast and written informed consent was obtained from each patient's legal guardian before enrolment in the study; assent was also obtained from children ≥8 years. Samples and patient data were collected prospectively from 23 neonates/infants/children who received intravenous K-canrenoate as part of their care in the NICU at the Royal Jubilee Maternity Service, Belfast or in the medical and intensive care wards at the Royal Belfast Hospital for Sick Children. Dosage regimens used were those deemed appropriate by the treating clinicians.

A maximum of eight samples were collected from each patient, usually when blood was being withdrawn for routine laboratory analyses. However, ethical approval allowed additional samples to be taken at the discretion of the research nurse provided an indwelling catheter was in place. Blood samples, collected in EDTA sample tubes, were centrifuged at 1800g for 10 min; the plasma fraction was transferred to a clean sample tube and stored at -20°C until analysis.

Data on date and time of sampling and date and time of previous K-canrenoate doses were recorded for each sample. The following data were collected from each patient's medical notes: weight (WT), gestational age (GA), postnatal age (PNA), gender, serum creatinine, serum albumin, haematocrit and concomitant medications.

Response to treatment

In order to assess effectiveness of K-canrenoate treatment, the following pharmacodynamic measures were recorded for all patients at the time of each sample: respiratory rate, heart rate, mean blood pressure and sodium and potassium levels. Furthermore, the association between these measures and measured canrenone concentrations were examined.

Drug analysis

A selective and sensitive HPLC method with UV detection for measuring plasma concentrations of canrenone, the active metabolite of K-canrenoate, was developed and validated[10]. The limits of detection and quantification were 6.0 ng/mL and 25.0 ng/mL respectively. Intra-day accuracy (mean RE%) ranged from -1.7 to +6.0% while the imprecision lay between 2.1 and 11.4% relative standard deviation (RSD). Inter-day accuracy ranged from -7.2 to +4.8%, with imprecision between 2.4 and 12.6% RSD.

Population pharmacokinetic modelling

Population pharmacokinetic analysis was performed by means of nonlinear mixed-effect modelling using first-order conditional estimation with interaction (NONMEM® version VI, level 1.0)[11].

Step 1

The complete dataset was used for development of the pharmacokinetic model. Potential models considered were classical linear one-and two-compartment models. The pharmacokinetic parameters estimated from these models (implemented using PREDPP subroutine ADVAN6) were CL/F and V/F for canrenone and the metabolic transformation rate constant of K-canrenoate into canrenone (K_f). The relationship between the parent drug and its metabolite was defined according to the following equations:

$$\frac{\text{d A(K-canrenoate)}}{\text{dt}} = -k_f \times \text{A(K-canrenoate)}$$

$$\frac{\text{d A(canrenone)}}{\text{dt}} = k_f \times \text{A(K-canrenoate)} - k_e \times \text{A(canrenone)}$$

Where k_f is the metabolic transformation rate constant of K-canrenoate into canrenone and k_e is the elimination rate constant of canrenone. Canrenone can be converted back to canrenoic acid through hydrolysis or be further metabolised and excreted in urine (see Figure 1). The pharmacokinetic parameters estimated here were based on the assumption that the total dose of K-canrenoate is converted into canrenone.

Interindividual variability (IIV) in each pharmacokinetic parameter (CL/F and V/F) was estimated using an exponential scale since they must be constrained to be greater than zero and their distribution is often right skewed[12].

Proportional and additive components of residual variability were estimated throughout model development, as follows:

$$C_{ij} = C_{pred,ij} \times \left(1 + \varepsilon_{p,ij}\right) + \varepsilon_{A,ij}$$

Simplification was considered during the model building by deleting the residual variance component with a value close to zero.

Weight was included as an *a priori* covariate on CL/F and V/F in the basic pharmacokinetic model and was scaled to 70 kg. Values were adjusted for weight using fixed exponents of 0.75 for CL/F and 1 for V/F as follows[13-14].

$$\text{CL/F}_i = \theta_{CL} \times \left(WT_i / 70\right)^{0.75}$$

$$\text{V/F}_i = \theta_V \times \left(WT_i / 70\right)$$

However, and due to the fact that most of the children in the present study were neonates and infants less than 1 year-old, the allometric model exponents were also experimentally determined as additional thetas (**θ**s) and the results compared with those obtained when fixed exponents were used.

Step 2

Visual examination of scatter plots (or box-and-whisker plots in the case of categorical covariates) of individual Bayesian estimates and IIV variability (ETAs) obtained for each pharmacokinetic parameter from Step 1 versus each covariate were used to help identify whether the pharmacokinetic parameter might be significantly related to the covariate. Direct covariate testing was then performed to see if this relationship was significant.

Step 3

The final model was established using the forward inclusion–backward elimination method[15]. Forward inclusion of a covariate required a reduction in the minimum value of the objective function (MOFV) of at least 6.63, (p<0.01, df=1). During stepwise backward elimination a more stringent criterion of statistical significance was required and a covariate was retained in the model only if the MOFV increased at least 10.83 units (p<0.001, df=1) when removed.

Graphical inspection of goodness-of-fit was used throughout model building and evaluation[16]. Visual predictive check (VPC) plots were generated using PsN (http://psn.sourceforge.net) and plotted using Xpose® (http://xpose.sourceforge.net) to assess the deviations of model-predicted from observed concentrations when fixed or experimentally-determined exponents were used. In addition, internal validation of the final model was undertaken using the technique of bootstrapping (Wings for NONMEM, version 611, http://wfn.sourceforge.net/index.html).

Influence analysis

Influence analysis was carried out to assess stability of the final model parameters towards influential subjects[17]. This involved generating a series of new datasets where a unique subject was removed from each one (i.e. jack-knifed datasets). The final model was re-fitted to each of the new datasets. The percent change in parameter estimates obtained from each dataset, relative to parameter estimates obtained from the original dataset, was then calculated.

To test the overall influence of any individual on the model parameters, the jack-knifed matrix of structural model parameters and variance components was subjected to principal component analysis (PCA)[17] using SPSS® (version 17.0) for Windows.

Statistical Analysis

Univariate analysis was performed using SPSS® for windows (version 17.0; SPSS Inc., Chicago, IL, USA). The Spearman Rho (ρ) test was performed to determine the association between the various pharmacodynamic measures recorded at each sampling time and canrenone plasma concentrations. Two-tailed p-values of <0.05 were considered statistically significant.

Results

Patients and Data Collection

A total of 23 paediatric patients with a median body weight of 4 kg (2.16-28.0 kg) were enrolled in the study. Characteristics of the study subjects are presented in Table 1; 20 patients were <1 year, the others being 2, 6 and 10 years. The pharmacokinetic analysis was carried out on the complete data set without excluding any of the patients. The final population pharmacokinetic model obtained from the original dataset, however, was re-fitted to a reduced dataset which contained only children < 1 year-old to examine the

influence of older patients on predicted CL. The population pharmacokinetic parameter estimates obtained from the two datasets were then compared.

Response to Treatment

In patients with congestive heart failure, the measured concentrations of canrenone were significantly associated with reduced mean blood pressure (p=0.003), a sign of improvement in heart failure. On the other hand, in cases where K-canrenoate treatment was administered for management of retained fluids in the intensive care unit, measured levels of canrenone were significantly associated with reduced sodium levels (p<0.001) and increased levels of potassium (p=0.037) reflecting a good response to treatment in these patients.

Pharmacokinetic Modelling

NONMEM analysis was performed using 101 plasma concentrations from the 23 infants enrolled. **Figure 2** shows the individual plasma canrenone concentrations against time relative to drug administration. The one-compartment model with first order metabolite formation and elimination adequately described the disposition of canrenone in plasma. The limited number of samples collected shortly after K-canrenoate administration did not enable accurate evaluation of the distribution phase and hence the 2-compartment model did not provide a better fit to the data.

Since the additive term of residual error variance approached 0, it was removed resulting in a proportional error model that was considered adequate to describe residual variability. Only diagonal elements of the covariance matrix were estimated as population parameters were not highly correlated and exploration of the full covariance matrix resulted in a negligible decrease in MOFV.

Weight was included as an *a priori* covariate on clearance and volume using both

allometric scaling with fixed and experimentally-determined power values. Investigation of models where the power values were not fixed, but included as additional thetas (**θ**s), did not result in any significant improvement in model fit (Table 2). On the other hand, visual predictive checks created from these models showed slight model under-prediction of carenone measured concentrations when exponents were determined separately (as two different thetas) or when one theta value was chosen for both CL and V exponents (Figure 3). Therefore, fixed exponents of 0.75 for CL and 1 for V were used in the present study. From the VPC plot, it appears that the model with fixed exponents exhibited no evidence of misspecification.

Covariate screening and selection of the final model

Initial screening did not reveal any potential strong relationships between either CL/F or V/F and any of the covariates. However, some plots showed two extreme values related to the two oldest patients. None of the age descriptors (GA, PNA, PMA) showed any significant effect when included in the base model. This is to be expected, since age and weight are known to be highly correlated covariates[18].

The final population pharmacokinetic model for disposition of canrenone in plasma was therefore the base model that included weight as an *a priori* covariate as shown:

$$\text{CL/F (L/h)} = \theta_{CL} \times \left(\frac{\text{WT}}{70}\right)^{0.75} \quad \text{and} \quad \text{V/F (L)} = \theta_{V} \times \left(\frac{\text{WT}}{70}\right)$$

where θ_{CL} and θ_{V} are the typical population estimates of CL/F and V/F in a hypothetical individual with weight (WT) equal to 70 kg. The condition number of the final model was adequate (24.48) indicating that the model estimates were stable and not influenced by ill-conditioning. The mean parameter estimates and their variances are presented in Table 3.

Typical population estimates of CL/F and V/F were 11.4 L/hr/70 kg and 374.2 L/70 kg, respectively. The median weight in our population was 4kg; the corresponding values of CL/F and V/F in a 4 kg patient were therefore 1.33 L/hr and 21.4 L, respectively, with an elimination half-life ($t_{1/2}$) of 11.2 hr.

The IIVs (CV%) associated with CL/F and V/F in this model were 41.1% and 45.8% respectively. The residual variability (CV%) was 34.1%.

The median, 5th and 95th percentiles, mean (standard deviation) and range of the empirical Bayesian estimates for CL/F and V/F in the study population (obtained from the final model) are shown in Table 4. The table also shows weight normalised values for these parameters and the predicted elimination $t_{1/2}$. A review of the Bayesian estimates of CL for children older than 1 year, revealed that the oldest and the heaviest child within the group (10 years old, WT=28 kg) had the maximum value of predicted CL (7.38 L/hr). The other two patients, however, were not identified as having different CL from the rest of the population (estimated CL values were 3.6 and 2.9 L/hr for the 2 and 6 year-old patients, respectively).

Model evaluation and validation

Graphical evaluation

Agreement between measured and model-predicted canrenone concentrations final models is illustrated in Figure 4. Plots from the final model are randomly scattered with no systematic deviation from the line of identity indicating that the model characterizes the overall behaviour of the data.

Examination of residuals (Figure 5) indicates that the assumption of random effects was appropriate since both residuals and weighted residuals did not show any trend and were evenly distributed around zero in plots obtained from the final model. In addition,

almost all weighted residuals were contained within values of ±2 units of the null ordinate indicating absence of any influential observations.

Influence analysis

No subject had any profound effect on the model parameters. Generally, a subject may be considered influential when their removal from a dataset results in more than ±20 % change in parameter estimates[17]. In addition, no significant change in parameter estimates was seen when the final model was refitted to a dataset that involved only patients younger than one year. The mean population estimate of CL/F was very similar to that obtained from the original complete data set and the estimate of V/F was ~7% less. Therefore, there was no evidence that these subjects need to be removed from the analysis and the model was considered generally stable.

Since the number of estimated parameters in the final model was not high, the generated matrix of standardized parameters (fixed effects and variance components) did not allow principle component analysis (PCA) to be carried out on each component alone[19]. However, when PCA was performed on the full matrix of parameters, no influential individuals were identified, confirming the results obtained above.

Model validation

Results from 1,000 bootstrap re-sampled datasets, for which 996 models converged successfully, are presented in Table 3 indicating that model parameters and variance components were precisely estimated with acceptable % difference (<15%).

Lactonisation

The transformation rate constant of K-canrenoate into canrenone, k_f was estimated as 5.25 hr^{-1}, which represents a lactonisation $t_{1/2}$ of 0.13 hr (7.8 min) and the elimination rate constant of canrenone, k_e was estimated as 0.062 hr^{-1}. These results indicate that

lactonisation occurred rapidly in paediatric patients. Based on these values, the time to reach maximum concentration of canrenone (*Tmax*) would be 0.85 hr (51 min); previously reported values of lactonisation $t_{1/2}$ and time to reach maximum canrenone concentration in adults have been reported as 8±4 minutes and 29±15 minutes, respectively[20].

Discussion

Using a sparse sampling approach, pharmacokinetic analysis of canrenone plasma concentration data, obtained following IV administration of K-canrenoate to neonates, infants and children, we have shown that disposition of canrenone is affected by weight of the patient. Weight influenced both CL/F and V/F using the power allometric model with fixed exponents (0.75 for CL/F and 1 for V/F).

The IIV in CL/F and V/F was reduced from 69.64% to 41.06% and from 69.24% to 45.76%, respectively by inclusion of weight in the model. However, none of the other studied covariates reduced IIV further; this may be due to the narrow range or uneven distribution of these covariates in the studied population.

The population estimate for V/F in this study was 374.2 L (bodyweight 70 kg) which is much larger than plasma volume indicating that canrenone readily distributes into body tissues.

The population estimate of canrenone plasma clearance in paediatric patients obtained in the current study (11.4 L/hr when scaled to a weight of 70 kg) is lower than previously reported values in adults (17.6±7.6 L/hr/70 kg)[20]. This indicates that there are age-related differences in canrenone clearance probably due to reduced renal and hepatic function, and a lower activity of the enzymes responsible for metabolism of canrenone in infants.

Besides, in the study by Krause *et al* [20], the researchers suggested that the disposition of

canrenone in plasma in adults is triphasic, since a rapid α-phase ($t_{1/2}$ = 41 min) was observed in one volunteer, a β-phase ($t_{1/2}$ = 4 hr) was observed in all study volunteers (n=3) and a slow γ-phase ($t_{1/2}$ = 10.5 hr) was observed in one volunteer. The estimate of canrenone $t_{1/2}$ in plasma observed in the current study is higher than those previously reported values in adults. However, the results cannot be directly compared because of differences in the modelling approach and research methodology.

When K-canrenoate is administered intravenously it is instantaneously converted in the body to canrenoic acid which is then either converted to the biologically active metabolite canrenone, or glucuronidated and excreted in the urine. Since canrenone was detected in all patients and the estimated lactonisation rate constant was comparable to that previously reported in adults, these findings indicate that plasma paraoxonase enzymes (PONs) responsible for lactonisation of canrenoic acid to canrenone (i.e. PON1 and PON3) are active in paediatric patients, including neonates. PON3 is also responsible for hydrolysis of spironolactone and canrenone.[21] Genetic variation plays a role in determining levels of activity of PONs[22] and serum PON1 activity is low at birth but increases to a plateau between 6 and 15 months of age[23]; both factors will therefore contribute to interindividual variability. Although we are unaware of reports regarding PON3 in children, our results suggest that it may be active in neonates and infants.

In the present study, only K-canrenoate was administered and neither concentrations of parent drug nor concentrations of its glucuronidated metabolite were measured. To allow all parameters to be characterised in such a reversible system would require both K-canrenoate and canrenone to be administered separately; concentrations of the two compounds could then be measured and the four concentration-time profiles evaluated[24]. This was not possible in the current research which was carried out within a normal clinical environment. In the present modelling, it was therefore necessary to assume that K-canrenoate was irreversibly converted to canrenone and estimated values of

clearance and volume were based on the assumption that the total dose of K-canrenoate was converted to canrenone. These estimated values should therefore be regarded as the upper limits of the true values.

Conclusion

The range of estimated CL/F in the study population was 0.67 - 7.38 L/hr, with the variance driven largely by body weight. The current practice of administering K-canrenoate according to body weight therefore appears to be justified in the paediatric population.

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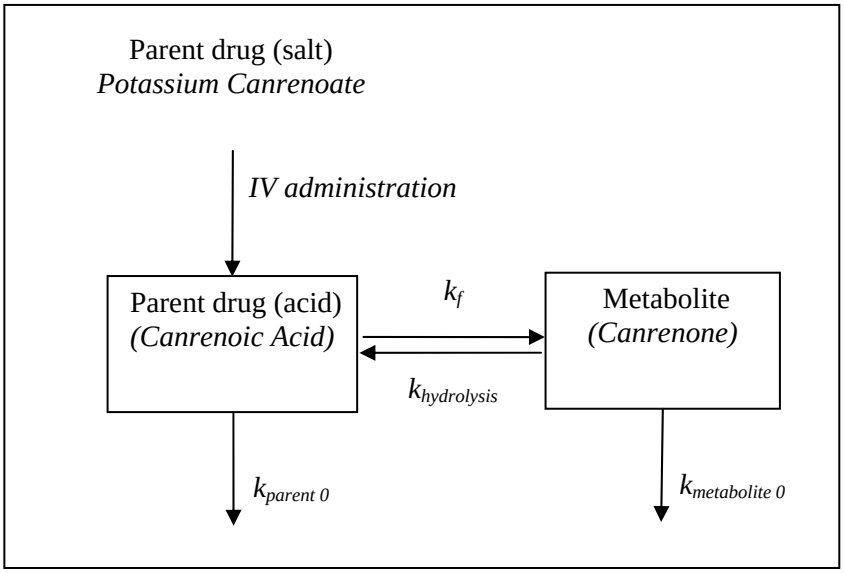

Figure 1: Representation of the reversible metabolic conversion of canrenoic acid to canrenone

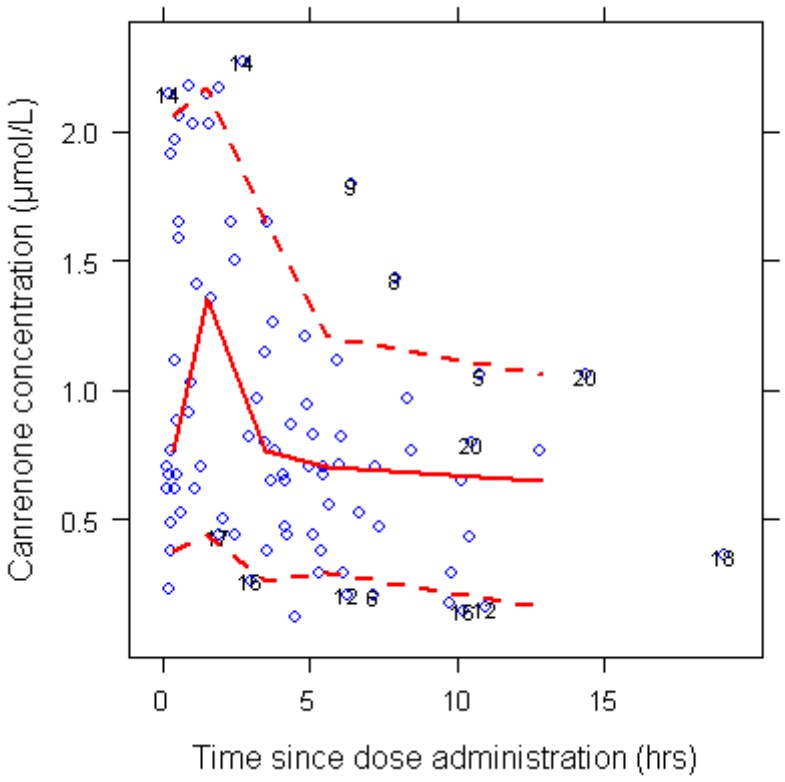

Figure 2: A plot of measured canrenone plasma concentrations versus time since dose administration. The solid thick line indicates the 50th percentile of measured plasma concentrations while the dashed lines indicate the 5th and 95th percentiles.

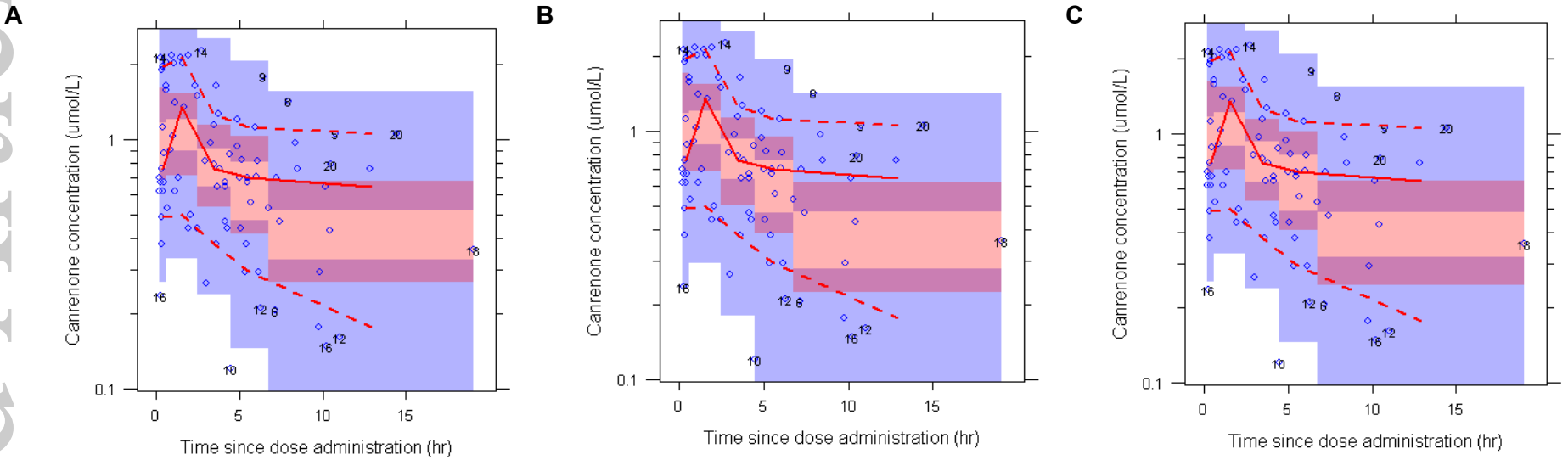

Figure 3: Visual predictive check plots for models using fixed and experimental exponents; (A) a model with fixed exponents of 0.75 for CL and 1 for V (B) a model with two experimentally determined thetas (one for each exponent) (c) a model with one experimentally theta for both exponents. Solid (–) and dashed (--) lines indicate the median, 5th and 95th percentiles for the observed concentrations (○). Shaded areas represent the upper, middle and lower CI for the 90% prediction intervals of simulated values (n=1000 per each patient time-point).

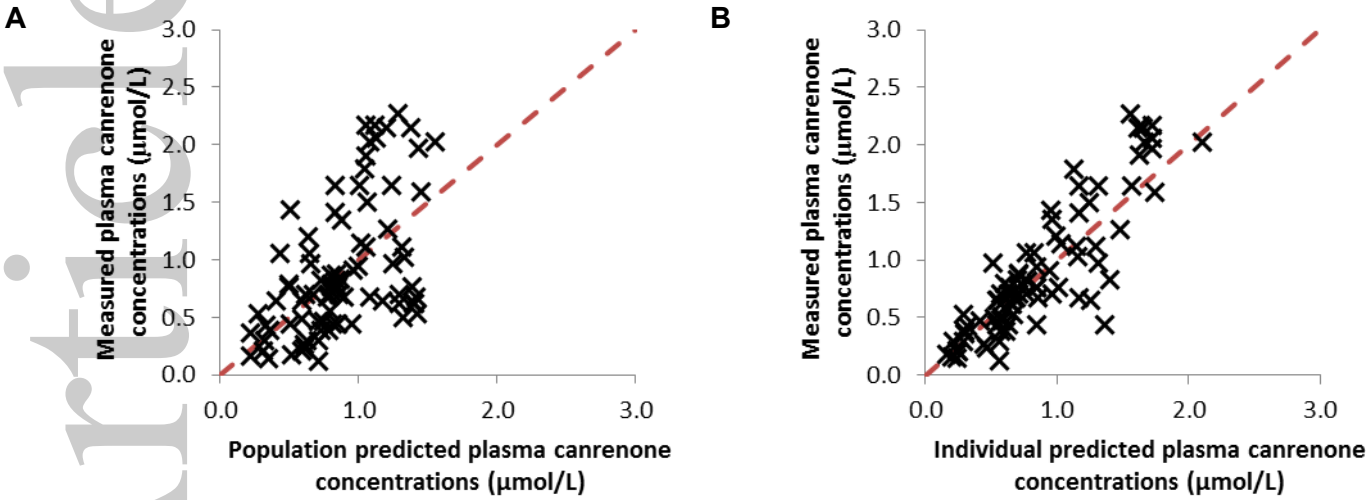

Figure 4: Plots of measured versus population predicted (PRED; A) and individual predicted (IPRED; B) plasma canrenone concentrations from the final model. The dashed line indicates the line of perfect agreement.

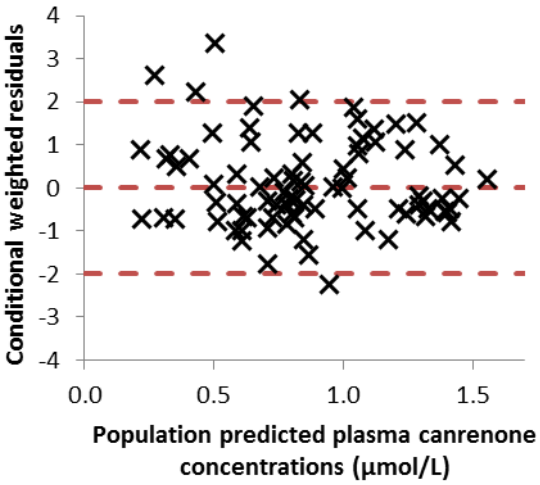

Figure 5: Plot of conditional weighted residuals (CWRES) versus population predicted plasma canrenone concentration (PRED) from the final model

Table 1: Characteristics of patients included in the study (n=23)

Characteristic		Value
		mean (range)
Number of patients		23
Number of samples		101
Number of samples per patient		4 (1-8)
K-canrenoate dose (µmol)		10.06 (3.77 - 70.43)
Measured canrenone conc. (µmol/L)		0.85 (0.12 - 2.26)
GA at birth (wk)[(a)]		37 (25 - 41)
PNA at inclusion	**(day)**[(a)]	71 (2 - 3738)
	(yr)	0.195 (0.005 - 10.241)
PMA at inclusion (wk)[(a)]		46.4 (37.3 - 574.0)
Weight at inclusion (kg)		4.00 (2.16 - 28.00)
Serum creatinine at inclusion (µmol/L)		32 (16 - 56)
Serum albumin at inclusion (mg/dL)		33 (29 - 40)
Haematocrit (%)		33 (26 - 40)
Gender	Male:Female	15:8
Indication for K-canrenoate	[1]Heart failure	8 (34.8%)
	[2]PICU treatment of retained fluids	15 (65.2%)
GA group	[1]Very preterm (<32 wk)	2 (8.7%)
	[2]Preterm (32 – <37 wk)	9 (39.1%) all at 36 wk
	[3]Full-term	12 (52.2%)

Continuous variables are presented as median (range).

Categorical variables are presented as number (percentage)

[(a)] GA, gestational age; PNA, postnatal age; PMA, postmenstrual age which is normally 2 weeks longer than the post-conceptional age (the sum of GA and PNA).

Table 2: Canrenone population parameter estimates from models using fixed and experimentally determined exponents

Parameter		Model with fixed exponents (θ_1 = 0.75 and θ_2 = 1)		Two experimentally determined θs (one for each exponent)		One experimentally determined θ (θ_1 for both exponents)	
		Estimate	CV%	Estimate	CV%	Estimate	CV%
MOFV		-98.56	-	-98.46	-	-97.85	-
CL/F (L/hr/70 kg)	$\theta_{CL/F}$	11.4	10.3	12.73	26.71	14.13	38.76
V/F (L/70 kg)	$\theta_{V/F}$	374.2	20.04	519.8	69.21	242.3	47.39
k_f (hr^{-1})	θ_{kf}	5.25	57.84	4.48	51.11	5.79	60.01
$IIV_{CL/F}$ (CV%)	$\omega_{CL/F}$	41.06	44.25	39.4	38.7	41.67	43.83
$IIV_{V/F}$ (CV%)	$\omega_{V/F}$	45.76	60.06	97.29	42.23	44.82	78.78
CL/F exponent	θ_1	0.75	-	0.798	11.92	0.833	16.44
V/F exponent	θ_2	1.0	-	1.07	26.05	-	-
Residual (CV%)	σ_{prop}	34.07	23.08	31.83	23.31	34.17	23.25

Model used: $\mathrm{CL/F\ (L/h)} = \theta_{CL} \times \left(\frac{\mathrm{WT}}{70}\right)^{\theta 1}$ and $\mathrm{V/F(L)} = \theta_{V} \times \left(\frac{\mathrm{WT}}{70}\right)^{\theta 2}$

θ_1 and θ_2 are the allometric model exponents; either fixed or experimentally determined.

$\omega_{CL/F}$ = interindividual variability in CL/F

$\omega_{V/F}$ = interindividual variability in V/F

σ_{prop} = residual variability (proportional error model)

CV%, percentage coefficient of variation

Table 3: Canrenone population parameter estimates from the final model developed from dataset of 23 patients, and mean parameter estimates from the final model fitted to the 1000 bootstrap samples

Parameter		Final Pharmacokinetic model		1000 Bootstrap Samples		
		Estimate	CV%	Mean	CV%	% diff
CL/F (L/hr/70 kg)	$\theta_{CL/F}$	11.4	10.3	11.39	11.32	-0.07
V/F (L/70 kg)	$\theta_{V/F}$	374.2	20.04	396.20	27.28	5.88
k_f (hr^{-1})	θ_{kf}	5.25	57.84	5.96	59.56	13.59
$IIV_{CL/F}$ (CV%)	$\omega_{CL/F}$	41.06	44.25	40.76	30.72	-0.73
$IIV_{V/F}$ (CV%)	$\omega_{V/F}$	45.76	60.06	52.03	69.84	13.69
Residual (CV%)	σ_{prop}	34.07	23.08	32.20	14.00	-5.48

Final model: $\mathrm{CL/F\ (L/h)} = \theta_{CL} \times \left(\frac{\mathrm{WT}}{70}\right)^{0.75}$ and $\mathrm{V/F(L)} = \theta_{V} \times \left(\frac{\mathrm{WT}}{70}\right)$

$\omega_{CL/F}$ = interindividual variability in CL/F

$\omega_{V/F}$ = interindividual variability in V/F

σ_{prop} = residual variability (proportional error model)

CV%, percentage coefficient of variation

% difference = $\frac{\text{bootsrap mean estimate} - \text{final model estimate}}{\text{final model estimate}} \times 100$

Table 4: Individual Bayesian estimates obtained from the final model

Parameter	Median	P_5	P_{95}	Mean ± SD	Range
CL/F (L/hr)	1.33	0.68	7.04	1.87 ± 1.56	0.67 - 7.38
V/F (L)	19.62	13.16	193.65	34.00 ± 42.95	13.14 - 207.06
$t_{1/2}$ (hr)	12.09	4.38	19.57	12.12 ± 4.34	4.14 - 19.58
CL/F (L/hr/kg)*	0.32	0.16	0.71	0.35 ± 0.14	0.16 - 0.73
V/F (L/kg)*	5.35	3.35	7.80	5.36 ± 1.18	3.28 - 7.85

P_5, 5th percentile; P_{95}, 95th percentile

SD, standard deviation

*calculated using the weight of each individual